Clinical Genetics At A Populational Level
The Ethnicity of Disease in the United States*

*Victor A. McKusick, M.D.***

I have chosen to alter the title of this presentation to read: Clinical Genetics at a Populational Level, with a subtitle: The Ethnicity of Disease in the United States. Lest anyone think he has been drawn here on false pretenses, let me hasten to state that what I am going to talk about is the same as it would have been under the previous title. I hope that talking about the ethnic distribution of disease in the United States is not too parochial an approach for this international seminar.

Except for the Indians among us, we Americans have come here from all parts of the globe, in the last four or five centuries, more from some parts than from others. Furthermore, despite the melting pot metaphor we have remained to a considerable extent in separate groups according to ethnic extraction. In part this is a consequence of the fact that insufficient time has elapsed for mixing, but in an appreciable degree is attributable to religious and other social impediments to mixing. That people of different extractions differ in many physical characteristics and that many of these differences are based on differences in genetic constitution are matters that no one can dispute. Genetic differences extend, of course, to differences in the frequency of pathogenic genes. Because of the genetic diversity of the American people, different groups are likely to show differences in frequency of given diseases. The frequency of Mendelizing, that is, simply inherited disorders, is likely to vary among different groups and indeed for a number of examples is known to do so. Furthermore, differences in the frequency of common disorders of multifactorial causation, that is, those in which genetic factors are involved as contributing or susceptibility factors, are to be expected, although the genetic basis of interethnic differences is harder to establish in these cases because it is never certain that environmental factors, which are also involved, are identical in the groups compared.

I am using the word *ethnic* here in the general sense to indicate both racial grouping and social grouping. Since the two, one biologically based, one culturally based, are essentially always indistinguishable, one term may be indicated. Coming from the Greek word for nation, *ethnic* furthermore avoids the odium of *race* and has sufficiently general connotations to be appropriate in the usage here.

A study of the ethnicity of disease has practical usefulness in diagnosis and management and it has usefulness, for example, in the design of screening programs. It has potential usefulness to genetic theory by providing the points of departure for study of factors which influence the frequency of genes in populations.

Research on the ethnic distribution of disease can take three or four different approaches. In the first place a specific ethnic group can be surveyed for all disease. This is the approach, for example, that we have used in the Old Order Amish, although they have characteristics, particularly as regarding inbreeding which distinguishes the

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**Professor of Medicine; Chief, Division of Medical Genetics, Department of Medicine, Johns Hopkins University School of Medicine and Johns Hopkins Hospital, Baltimore, Maryland 21205.

group from most other American ethnic groups. In the second place, total ascertainment or random ascertainment of cases of a specific entity can be attempted for a given area, and the ethnic extraction of the patients determined. This approach we have used in connection with homocystinuria and with Riley-Day dysautonomia, and I will describe those studies to you.

A third approach combines the first two. A genetic survey of a given population composed of several genetic stocks, such as we have in most areas of this country, can be made, and the frequency of diseases in the various components of the population compared. This approach we have initiated on a modest scale in Washington County, Maryland. This county has been the subject of various epidemiologic studies for close to 40 years. It has a relatively stable population of about 100,000, about half of which is in the urban county seat of Hagerstown, the other half living in small villages and on farms. Advantages of Washington County for total survey of this type include the fact that one hospital provides the majority of care. An early result of a survey of neurologic disorders in Washington County is the finding of a relatively large number of cases of a dominantly inherited type of amyloidosis, perhaps identical to that described by Rukavina and colleagues (1956) in an enclave of Swiss origin in Indiana. The Washington County cases are of pre-revolutionary German immigrant extraction. In connection with the study of amyloidosis in the Washington County group, we have been impressed with the fact that a total population survey has brought to light cases which clearly represent the same entity but were considered separate entities previously. Because of the rather variable manifestation of dominantly inherited amyloidosis of this type, these cases previously existed under the guise not only of a progressive neuropathy but also of arthropathy because of the pain and stiffness of the hands resulting from the carpal tunnel syndrome.

A fourth approach to the study of ethnicity in disease, which has been used several times in this country, involves comparison of an ethnic group in this country with close relatives, or at least the same ethnic group, who remained in the country of origin. Thus, Japanese in the United States and Japan have been compared, Irish, Norwegians, Italians in the United States and Europe, and so on. This approach has been used in connection with common disorders, which at the best have complex genetics, but one can point to even more useful studies such as those involving the Mediterranean and African types of G-6-PD deficiency, the hemoglobinopathies, the recently studied adult intestinal lactase deficiency, a state of high frequency in the American Negro, all these having been studied in both the parent and the American population. Acatalasemia or at least hypocatalasemia, which has been so nicely studied in Japan by Hamilton and his colleagues (1961), could perhaps be studied with interesting findings in Japanese-Americans.

I shall confine the rest of my remarks to illustrations of the first two approaches: the total study of a specific ethnic group and the study of a specific entity as to ethnic distribution.

The Old Order Amish

When one studies genetic disease in a specific group, one should familiarize oneself with the characteristics which Professor Cavalli referred to as the genetic structure of the population and which Dr. Witkop also nicely illustrated. One should be familiar with the demographic history of the group in the Old World and with the history of migration (both the history of immigration and that of internal migration). One should be familiar with the sociologic factors such as religious and others which make either for dispersion or cohesion of the group and of course one should be familiar with the current demography of the group. The group that I would like to tell you a little bit about—it will come as no surprise to you—is the Old Order Amish.

I would like to begin a description of

Fig. 1. A pictorial essay on the sociology of the Amish.

the group by showing you my most prized picture (Fig. 1), which is a sort of pictorial essay on the sociology of the group. The group is well known, or at least widely known, because of their peculiar sociologic and technical practices in the midst of modern society (Hostetler, 1963). The married men wear beards but do not have mustaches. They wear a stylized form of dress.

All the Amish are rural living, and most of them are farmers. They do not use modern mechanized agricultural equipment but use horse-drawn equipment for the most part. They use the horse and buggy for transportation.

If there is one characteristic which distinguishes the Old Order Amish from other conservative Protestant sects with whom they are often confused, such as the conservative Mennonites, the Dunkards, and so on, it is the practice of the Old Order Amish to hold religious services in the home. They do not have meeting houses but hold religious services in the homes by rotation. They are opposed to higher education; they educate their children only to the minimum required by the state, and are opposed in general to consolidated schools, preferring the one-room schoolhouses, many of which are operated as parochial schools.

All the Amish now live in the United States or Ontario (Fig. 2). However, the sect originated in the Canton of Bern in Switzerland in 1693 as an offshoot from the older and more extensive Mennonite movement. Jacob Ammann, the Mennonite bishop who founded the sect, picked up converts among other Mennonites, particularly those who had left Bern to go to Alsace and Lorraine and the Palatinate. The Amish movement was a movement within a movement and genetically its adherents were mainly Bernese Swiss.

The Amish began coming to this country about 1720. A considerable portion of them, although the absolute numbers were small, came between 1720 and 1770; essentially all the Amish of Eastern Pennsylvania are of pre-revolutionary ancestry. Later waves of immigration continued until about 1850, the later immigrants seeking residence to the West. This difference in the details of the migration history probably has something to do with the fact that one today can recognize separate demes within the larger Amish group.

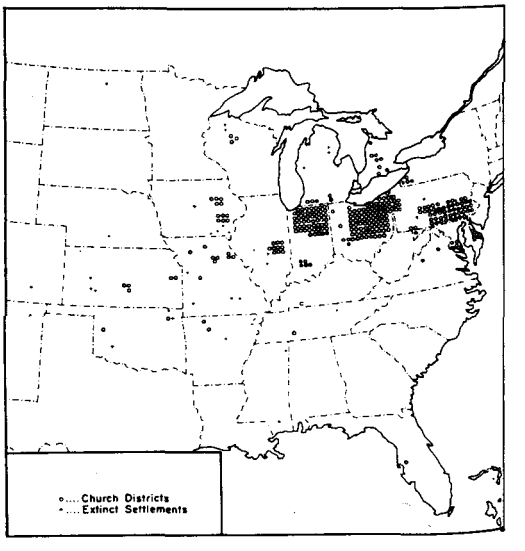

Fig. 2. Distribution of Amish settlements. From Hostetler.

Over 80% of the Amish live in three states, in Pennsylvania, Ohio and Indiana and over half the Amish live in three counties, Lancaster County, Pennsylvania, Holmes County, Ohio, and LaGrange County in northern Indiana. The two counties we have focused on most extensively are Lancaster County and Holmes County. These have been very useful for comparison purposes. The total Amish population is estimated to be in excess of 45,000 now. Each of these two counties, Lancaster and Holmes, has about 9,000 population. Lancaster County is close to us in Baltimore, so that we can get there in about an hour and a half, put in a good day's work and be home by a reasonable hour in the evening.

Table 1 presents a list of some of the characteristics of Amish society which render the group useful for some types of genetic study. In the first place, it is a defined population, a self-defined population. In the second place, it is a closed population. The Amish do not proselytize and for practical purposes no new blood has entered the groups since the immigrations. Origins in Western Europe are well known. Genealogical records are delightfully extensive. The standards of living and the standards of medical care are relatively high. There is a greater uniformity of socioeconomic circumstances than one usually encounters. There is a great, sometimes almost morbid, interest in illness. They are interested in what ails other Amishmen and partly because of their clannishness can tell you other Amishmen who have an ailment similar to the one you may be dealing with. The consanguinity rate, which we are in the process of quantitating, appears to be high. Illegitimacy rate is low. There is a certain amount of premarital conception, but the biological father, by all indications, in the overwhelming majority of instances, is the legal father. Families are large, averaging about eight children per family and the group is immobile. The families do not go off to cities to seek employment and so on. These are great advantages in genetic studies these days when so frequently families are scattered hither and yon. If one is studying mental retardation, as we have been, it is an advantage, too, that the Amish take care of their own at home. They do not institutionalize their retarded and other defectives.

TABLE 1

CHARACTERISTICS OF AMISH SOCIETY FAVORABLE FOR GENTIC STUDIES

1.	Defined population
2.	Closed population
3.	Well-known origins in western Europe
4.	Extensive genealogic records
5.	High standard of living
6.	Relatively high standard of medical care
7.	Uniform socio-economic, including occupational, factors
8.	Great interest in illness
9.	High consanguinity rate
10.	Low illegitimacy rate
11.	Clannishness
12.	Immobility
13.	Large families
14.	Institutionalization resisted

I shall next show you the evidence that in the overall Amish group one is dealing with a number of separate demes. I think this word "deme" is a rather useful one. It was introduced (in recent times, at any rate) by George P. Murdock (1948) to refer to consanguineal kin groups, or local endogamous groups and that is what these several Amish groups represent, the Lancaster County group being one, the Holmes County group being another, and so on. The evidence for the existence of separate demes is of at least four types: In the first place the migration history and the history since the migration; in the second place, the distribution of surnames; thirdly, the distribution of diseases, particularly the frequency of rare recessives in the separate groups; and fourthly, blood group differences. Table 2 compares the name fre-

TABLE 2

FAMILY NAMES

Holmes County, Ohio		*Lancaster County, Pa.*	
Miller	—26%	Stoltzfus	—23%
Yoder	—17%	King	—12%
Troyer	—11%	Fisher	—12%
Hershberger	— 5%	Beiler	—12%
Raber	— 5%	Zook	— 6%
Schlabach	— 5%	Lapp	— 7%
	69%		72%

quencies in Holmes County and Lancaster County. Six names in each case account for 70% of the population, but they are different sets of six names. When one gets down to names of lower frequency, there is some duplication in the two groups, but in the high frequency names, there are these differences. It is of interest that the name Stoltzfus accounts for one-fourth the Lancaster County Amish—interesting because there was only one Stoltzfus, Nicholas Stoltzfus, who immigrated in 1766 and who must have contributed disproportionately to the present gene pool, just as he gave his name to an unusually large proportion of the present population.

The following are examples of diseases which have relatively high frequency in four Amish groups which appear to represent separate demes. The Ellis-van Creveld syndrome (McKusick et al., 1964), which is a form of chondrodystrophy with polydactyly, dystrophy of the fingernails, and in about half the cases large atrial septal defect, occurs with unprecedentedly high frequency in the Lancaster County Amish. There we have 33 sibships in which at least one case of this condition has occurred and at the time these studies were reported there were more cases of this condition identified in Lancaster County than had been reported hitherto in all the literature put together. However, this condition has not been identified in Amish except those of eastern Pennsylvania.

In Mifflin County, Pennsylvania, which is another Amish group at the center of the state, pyruvate kinase deficiency hemolytic anemia (Bowman et al., 1965), about which you also heard yesterday, is unusually frequent. We now have 12 sibships with this condition. I think that a point that Professor Böök made is illustrated well by each of these conditions: the advantage of knowing that one is dealing with the same entity in each and all of these cases. There is an indication from the study in the Mifflin County Amish of heterogeneity in pyruvate kinase deficiency. The disease in this group is very severe and rather stereotyped in its severity. Jaundice and anemia are already evident at birth and may be quite severe, requiring exchange transfusion. Probably all cases die by age three years if not treated. Splenectomy has dramatically beneficial effects, converting the process into a compensated hemolytic state which does not require transfusion and is otherwise not incapacitating. The other cases of pyruvate kinase deficiency that have been described have, in many instances, been quite mild and not detected until adulthood.

In Holmes County, Ohio, hemophilia B, or Christmas disease, is quite frequent. This is an X-linked recessive, of course, but the argument here is the same. Hemophilia B has not been identified in eastern Pennsylvania Amish.

In Adams and Allen Counties, Indiana, the autosomal recessive limb girdle muscular dystrophy is quite frequent. This has been studied by Dr. C. E. Jackson of Bluffton, Indiana (Jackson and Carey, 1961). It is of interest that whereas in most series of cases of muscular dystrophy, the sex-linked form has been most frequent, such is not the case in the Canton of Bern, where the most frequent form is this limb girdle muscular dystrophy. I am sure the significance of this fact is evident to you.

We did a blood group frequency survey in the Lancaster County Amish, studying the blood groups of a random sample of individuals drawn from the census of the population. This was a random sample of married couples, these being taken to be as representative of individuals as little related as one finds in this group. However, when households were visited to get blood samples, anyone who would give a sample was also bled, so that the total sample was in excess of 700. The figures in Table 3 are on the random sample, although the total sample did not differ greatly. For comparison with the Lancaster County sample, we had ABO and Rh data on a group of Holmes County Amish. It may interest and amuse you to know how the Holmes County data were collected. Because of the high frequency of hemophilia B in the Holmes County group, the Amish appreciate the importance of blood trans-

TABLE 3

ABO PHENOTPE FREQUENCIES IN TWO OLD ORDER AMISH DEMES

	Canton Bern	*Holmes Co.*	*Lancaster Co.*	*So. England*
		N = 1027	*N = 215*	
0	.39	.34	.106	.44
A	.50	.54	.740	.45
B	.08	.06	.047	.08
AB	.03	.06	.107	.03

fusion and do give blood freely. So the Red Cross donor center had an extensive file. Holmes County is largely a rural county and the Amish constitute about 35 per cent of the population of the county. We had a complete tabulation of Amish surnames, so in going through the files, we could pick out Amish surnames; but since some non-Amish have the same surnames, we had the problem of distinguishing them. The ingenious method which was devised by Miss Minerva Stauffer, who did these studies, was to pick those individuals who had Amish names and who, on the donor card, had no telephone number recorded. The Amish do not have telephones and essentially everyone else has a telephone. Thus the 1027 Holmes County samples (Table 3) are on persons with Amish surnames and no telephone, if you will accept those as Amish!

The blood group data in Lancaster County show rather peculiar ABO frequencies with a very high type A frequency, three-fourths of the group being blood type A (see Table 3). We presume this represents drift but this is only a presumption. The Holmes County group has an ABO blood group frequency closer to those of the Bernese Swiss shown on your left. I might say that Rh negativity in both the Lancaster County Amish and the Holmes County Amish is relatively high, being about 25 per cent in both groups. There are many other interesting ramifications of the Lancaster County blood group study. There were some rare blood groups and one could, by genealogical tracing, identify the probable point of introduction of these genes into the population. There were other interesting aspects with reference to the correlation between blood type and family name and generational data, but I shall not take the time to go into those now.

You have heard reiterated several times, and very nicely illustrated, the fact that isolated inbred groups represent a happy hunting ground for medical geneticists because of the increased frequency of homozygotes for recessive genes. There is a popular notion that inbreeding causes a build-up of genes—usually it's said "a build-up of bad genes." Of course, as you are aware, inbreeding *per se* does not influence gene frequency. It influences genotype frequency because it increases the proportion of homozygotes, but I repeat, inbreeding *per se* does not change *gene* frequency. We have in many as compared to experimental species such as the mouse an anomalous situation, in that known autosomal dominants exceed known autosomal recessives, whereas in the mouse the converse is the case. Verschuer in 1959 estimated 285 autosomal dominant traits, 89 autosomal recessives. The precise figures are not too relevant; the ratio is what I am emphasizing here. Dr. Margaret Green in 1961 estimated for me that in the mouse 35 autosomal dominant mutations are known and about 123 autosomal recessive mutations. There are perhaps 300 mouse mutations now known, the ratio remaining the same.

If I may be permitted to do a little advertising: I have recently completed for publication catalogs of autosomal dominant and autosomal recessive and X-linked traits in man. Two "classes of citizens" have been maintained in the catalogs: first, those in which the particular mode of inheritance seems adequately established, and secondly, those in which the particular mode of inheritance has been suggested but as yet not proved. The inclusion of the latter seems important for heuristic purposes, so that we will keep our eyes open when similar cases come along. In recent years, the total number of autosomal recessives have been "coming up fast," mainly through the burgeoning of biochemical genetics and the description of new inborn errors of metabolism, but autosomal domi-

nants still exceed autosomal recessives. I list 269 dominants and 237 recessives as "proved." It is interesting to note that I was willing to accept fewer traits as proven autosomal dominant than was Professor Verschuer in 1959, but the figures are not very much different.

The studies in the Amish, like the studies of Dr. Witkop in tri-racial isolates and the studies of Professor Böök in Swedish isolates, have uncovered new recessives. For example, we have a form of dwarfism called cartilage-hair hypoplasia (McKusick et al., 1965), a chondrodystrophy in which the hair is fine and sparse. We have found a fatal variety of intrahepatic cholestasis in the Amish group. In a survey of major neurologic disease and mental retardation in the Holmes County group, two recessively inherited major neurologic disorders which by all indications have not been previously identified, have come to light, and there are other "new" recessives that I could cite. I think this type of pursuit requires no defense, but if it does, let me say that this should not be considered merely stamp collecting, that description of "new" entities provides information on what Lewontin referred to as "the mutational repertoire of man." These abnormalities are the indications we have of what the normal genetic constitution of man is like.

In both the Lancaster County and the Holmes County groups, total censuses have been assembled and in conjunction with these, total genealogies are well on the way to completion. By total genealogy we mean a tracing back to the immigrant ancestors as completely as possible of each and all members of the community. The purposes to which the total genealogy has been put are mainly two. One is in the calculation of coefficients of consanguinity and the second, in the determination of common ancestor of all parents of sibships carrying a given recessive disorder. In an inbred group such as the Lancaster County deme, which is a closed population and of which the number of founding fathers (and mothers) was relatively small, when one is dealing with an ordinarly rare gene such as the Ellis-van Creveld gene or the pyruvate kinase deficiency gene, it is logical to presume that only one of the founding fathers was a heterozygous carrier for that gene. Of course, a consideration that modifies that presumption is the frequent practice of brothers and other close relatives to immigrate together. This would increase the chance that more than one funding father was a carrier. In the case of a number of the conditions that we have studied in these populations, we have traced back the ancestry of each and every parent of all affected individuals, and have been able to identify that only one founding father (and mother) was shared in common by all parents. This is a matter that one can do very laboriously by hand but which is aided greatly by the computer. For example, in the 33 Ellis-van Creveld sibships this involved tracing back of the ancestry of 66 parents to identify the fact that only one immigrant ancestral couple, Samuel King and his wife, was shared by all these parents. In the case of pyruvate kinase deficiency, it was again possible to trace it back to one and only one immigrant ancestral couple, "Strong Jacob" Yoder and wife. This strengthens the idea that the condition is a recessive. It certainly strengthens the idea that one is dealing with one and the same entity in all the cases. (The chance that 66 Lancaster County Amish would by chance all trace their ancestry to Samuel King or that 24 Mifflin County Amish would all trace their ancestry to Strong Jacob is thought to be very low, but quantitation of this chance should probably be attempted by computer using the total genealogies.)

A study attempting total ascertainment of neurological disorders of major nature and mental retardation in the Holmes County group was conducted. There were, in addition to the forms of mental retardation that have certain clinically distinguishing features, although thus far no biochemical ones, some instances of familial, nonspecific mental retardation of severe degree. As mentioned earlier, "new" neurologic disorders were uncovered. Mongolism

was also studied in this group with karyotyping of all cases. Sixteen were found in the population and we estimate that this is not an abnormal frequency. It agrees closely with that found in outbred populations.

Common diseases can be studied usefully in closed populations such as this, and we have under study in the Amish 1) hypertension—that is, blood pressure, 2) diabetes mellitus, 3) congenital heart disease, and 4) cervical cancer. Cervical cancer came to light as a matter for special study because of a Papanicolaou program which has been under way in Holmes County for about twelve years, and in which an impressively lower frequency of cervical cancer was turned up in Amish women. This has been looked into further and seems to be a "true bill."

Homocystinuria

I shall move now to a consideration of a study of the ethnic distribution of two specific diseases. The first one that I shall talk about is homocystinuria, which is an inborn error of metabolism, simulating in many of its features the Marfan syndrome. In both the Marfan syndrome and homocystinuria the patients are often unusually tall and have ectopia lentis and chest deformity.

The cyanide nitroprusside screening test was used as the primary mode of ascertainment in the survey I will describe to you (Schimke et al., 1965). This test is, of course, also positive for cystine, so other means must be used for distinguishing the two. High voltage paper electrophoresis of the urines was the method used to distinguish cystinuria from homocystinuria.

We think that all patients with homocystinuria have ectopia lentis, by age 10 at any rate. The dislocation of the lenses seems to be progressive. We have a number of experiences where a patient has had competent ophthalmologic examinations early without this being detected. The progressive nature introduces an aspect of hope as far as being able to influence the disease by treatment. All the patients seem to have osteoporosis. They are prone to fractures also.

The patients with homocystinuria, like the patients with the true Marfan syndrome, have cardiovascular problems of major grade, but they are of a different character entirely, being thrombotic in nature, thrombosis in arteries and veins. We have seen thrombosis of both internal carotid arteries in 12-and 13-year-old children, death from coronary occlusion in persons, even females, in their teens or early 20's, thrombosis of the inferior vena cava, and recurrent thrombophlebitis of the legs complicated by pulmonary embolism.

Homocystinuria was first described in 1962 by a group in northern Ireland who had detected it in the course of a urine chromatography survey in institutions for the mentally retarded. Simultaneously it was described by Dr. Waisman in Madison, Wisconsin, who had studied the single case of a severely retarded infant. Because of this background, mental retardation was considered a hallmark of disease. This, in fact, proves not to be the case when a more appropriately selected series of cases is studied. Among homocystinurics ascertained by screening cases of ectopia lentis, over 40 per cent have unequivocally normal intelligence. Even in the same family retarded and unretarded homocystinurics may be observed. Take, for example, the family with affected brother and sister reported elsewhere (Schimke et al., 1965). Both have dislocation of the lenses and the brother in particular is quite tall and has chest deformity. He broke a leg after relatively minor trauma and thereafter developed thrombophlebitis with pulmonary embolus. He is of normal intelligence, graduated from a state teachers college and now teaches school. His sister is moderately retarded; she was unable to complete high school. In both of these sibs enzyme assays were done on liver biopsy material by Dr. Harvey Mudd at the NIH, with the demonstration that both had the very low levels characteristic of this disease, i.e., very low levels of cystathionine synthetase, which is the enzyme whose activity is deficient in this condition.

Facial flushing has been quite impressive,

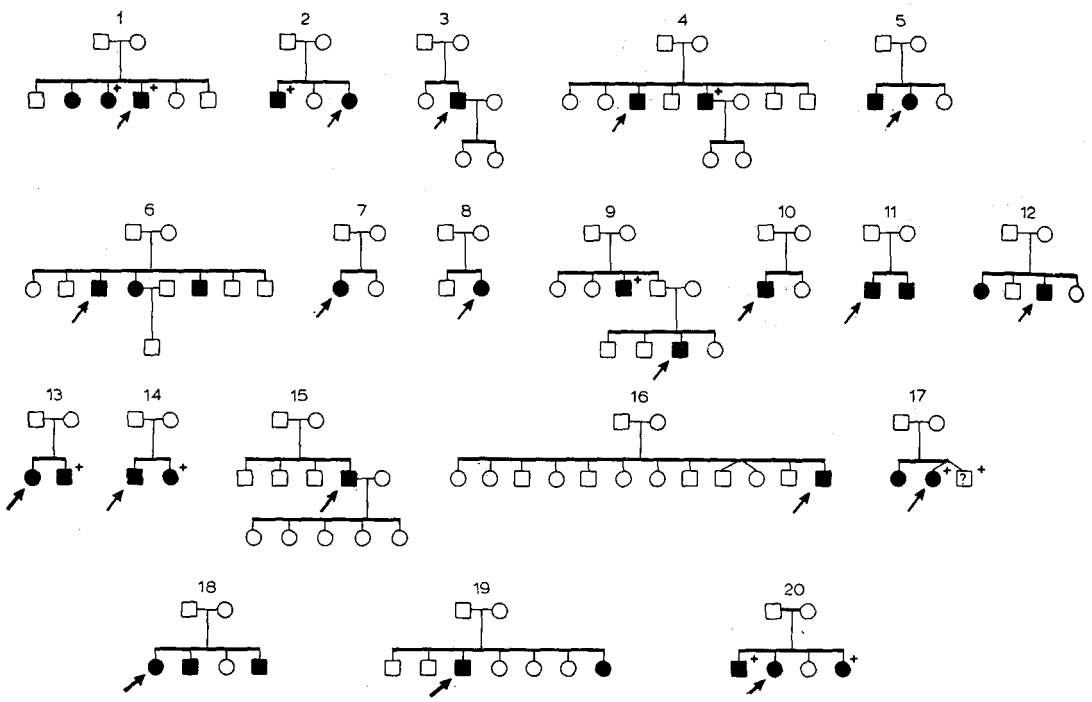

Fig. 3. Twenty families with homocystinuric members. From Schimke et al.

particularly in the British cases. I have wondered, not entirely facetiously, whether the lack of central heating had anything to do with the lesser impressiveness of flushed face in homocystinurics in the U.S., but we have at least one patient with a very red face. He is a dairy farmer and has exposure to the elements, but I think his face is redder than you would expect from that alone. He has dislocation of the lenses. He is six feet three inches tall, has chest deformity, hypertension, had had a myocardial infarction and is fibrillating. This man's parents were both born within a few miles of each other in the Dalarne area of Sweden and although they were not known to be related, we have suspicions. I would be interested to know whether Professor Böök knows if homocystinuria has been detected in Sweden. I am not aware of reports of this condition emanating from Sweden.

Now I am at last getting to the populational aspect of this disease. We undertook a screening program of all cases of dislocated lenses and/or presumed Marfan syndrome from which we could get urine. Urine samples could be easily sent in by mail. Arrangements were made with a large number of eye clinics over the country to screen cases in the categories mentioned. To date we have screened something in excess of 700 families, each with at least one case of this type, and have uncovered 35 sibships with patients with this condition. The total number of cases is 62, I believe. In Fig. 3 are fragmentary pedigrees of the first 20 families. Homocystinuria appears to be a simple recessive, like all other inborn errors of metabolism of the Garrodian type, and segregation analysis proves that this is the case.

The following is an analysis at the point when we had 50 cases distributed in 26 kindreds, with 28 sibships, two of the kindreds having two affected sibships. Thirty of the 50 were male. The ages of the living patients varied from 6 to 45 years. Ten had died, all of thrombotic complications, varying in age at death from 3 to 28 years. Using rigorous criteria and throwing into the retarded group anyone who was even suspiciously "dim," it was found that 22 of the 50 individuals were of normal intelli-

TABLE 4

COMPARISON OF HOMOCYSTINURIA AND THE MARFAN SYNDROME

	Homocystinuria	*Marfan Syndrome*
Inheritance	Recessive	Dominant
Skeletal abnormality	Osteoporosis, fractures, occasional arachnodactyly	Arachnodactyly and loose-jointedness more striking
Pectus excavatum or carinatum	Frequent	Frequent
Ectopia lentis	Present	Present
Vascular disease	Dilatation with thrombosis in medium-sized arteries and veins	Dilatation and/or dissection of aorta
Skin	Malar flush, livedo reticularis	Striae distensae
Mental retardation	Frequent	Absent

gence. Consanguinity was either proved or suspected in a number of instances, and the ethnic background of these cases was quite diverse. We were not impressed with any evidence of heterogeneity in ethnic background. Many northern European nationalities, southern Italians, Negroes and Jews were represented. We had no cases of Oriental extraction. On the other hand, we screened very few Oriental families.

Table IV compares the features, clinical and genetic, of homocystinuria with those of the true Marfan syndrome.

Familial Dysautonomia

The other condition that we are attempting to study on a total ascertainment basis is familial dysautonomia, and in this instance the ethnic homogeneity observed with the previous condition was not observed. This condition was first described in 1949 by Riley, Day, and colleagues, pediatricians at Columbia University. They noted early the striking preponderance of the disease in persons of Jewish extraction. The features of this disease are listed here. The babies often show abnormality right from birth with trouble feeding and swallowing. Partly because of this, perhaps mainly because of this, they get recurrent bronchopneumonia from aspiration. Lack of tears is an impressive feature. Insensitivity to pain, emotional lability, and breath-holding attacks with loss of consciousness occur. It has been demonstrated in this condition that there is an insensitivity of the respiratory mechanism to oxygen lack and CO_2 excess, so that these children can literally make themselves pass out by holding their breath. The children should not be allowed to swim under water, it is thought, because they may, as it were, forget to come up. They have episodic vomiting, unexplained high fever, skin blotching, excessive sweating, motor incoordination, postural hypotension, and paroxysmal hypertension such that a number of these patients have been explored for suspected pheochromocytoma. Progressive scoliosis is a feature. Among the clinical findings is also absence of the deep tendon reflexes. The facies is rather characteristic with transverse mouth and tendency to facial drooping.

Mental retardation is not an integral feature of this condition, as nearly as we can determine. There may be some retardation, but we think that it is secondary to dehydration, the high fever, or the breath-holding attacks with unconsciousness and not a part of the primary disease.

Some patients have large, swollen knees, which are quite painless, and represent, by all indications, Charcot neuropathic joints. This feature has not been previously noted, partly because older groups of patients have not been studied. These patients, I repeat, are relatively insensitive to pain and have absent deep tendon reflexes. X-ray shows destruction in the epiphysis; the x-ray changes of Charcot joint developing before closure of the epiphysis is quite different

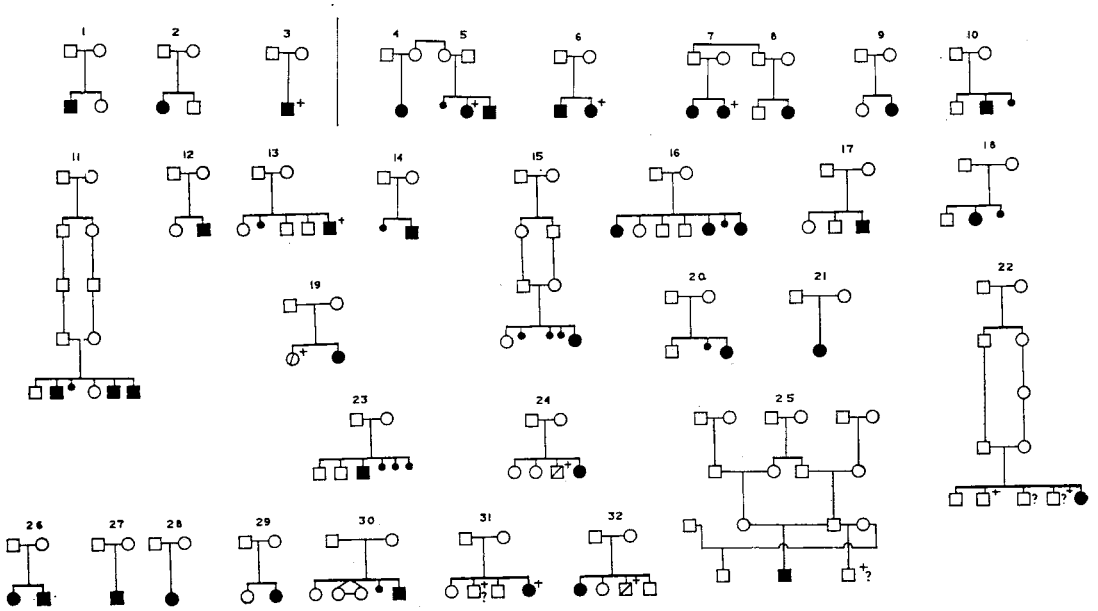

Fig. 4.-A 164 families in which one or more member has familial dysautonomia. From McKusick et al.

from that of Charcot joint occurring in an adult syphilitic, for example.

A consistent diagnostic sign in this condition is absence of the fungiform papillae from the tongue. The circumvallate papillae are also absent in most, perhaps

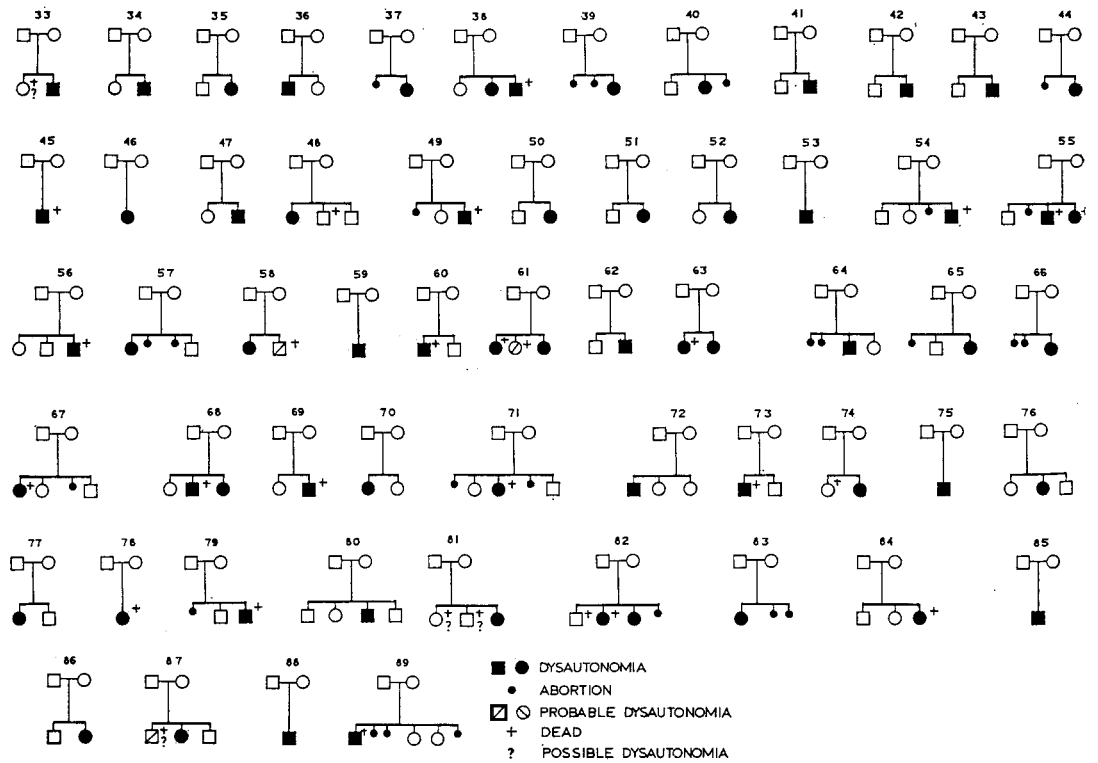

Fig. 4.-B

all of these cases; the filliform papillae are normal.

The ascertainment of families with this disorder was accomplished mainly through the Dysautonomia Association, which has an aggressive interest in this condition and for that reason an aggressive case-finding program. In addition, we communicated with a considerable number of pediatricians and pediatric neurologists to learn about other cases whenever possible. We have information about 220 families and thus far we have had a chance to visit and interview 164 of these families, and it is the findings in these that I shall tell you about. Figure 4A-D presents fragmentary pedigrees of these cases.

The Lenz-Hogben analysis on these families, which contain 200 cases, shows close agreement of the observed number with that expected of an autosomal recessive disorder assuming either complete or random ascertainment of families.

In these 164 families there are 200 affected, 91 male, 109 female. Sixty-seven of the cases are dead. In 162 of the families, both parents are of Jewish extraction. In two of the families, the mother ostensibly has no Jewish ancestry; the father is Jewish. Among the Jewish parents, there were only

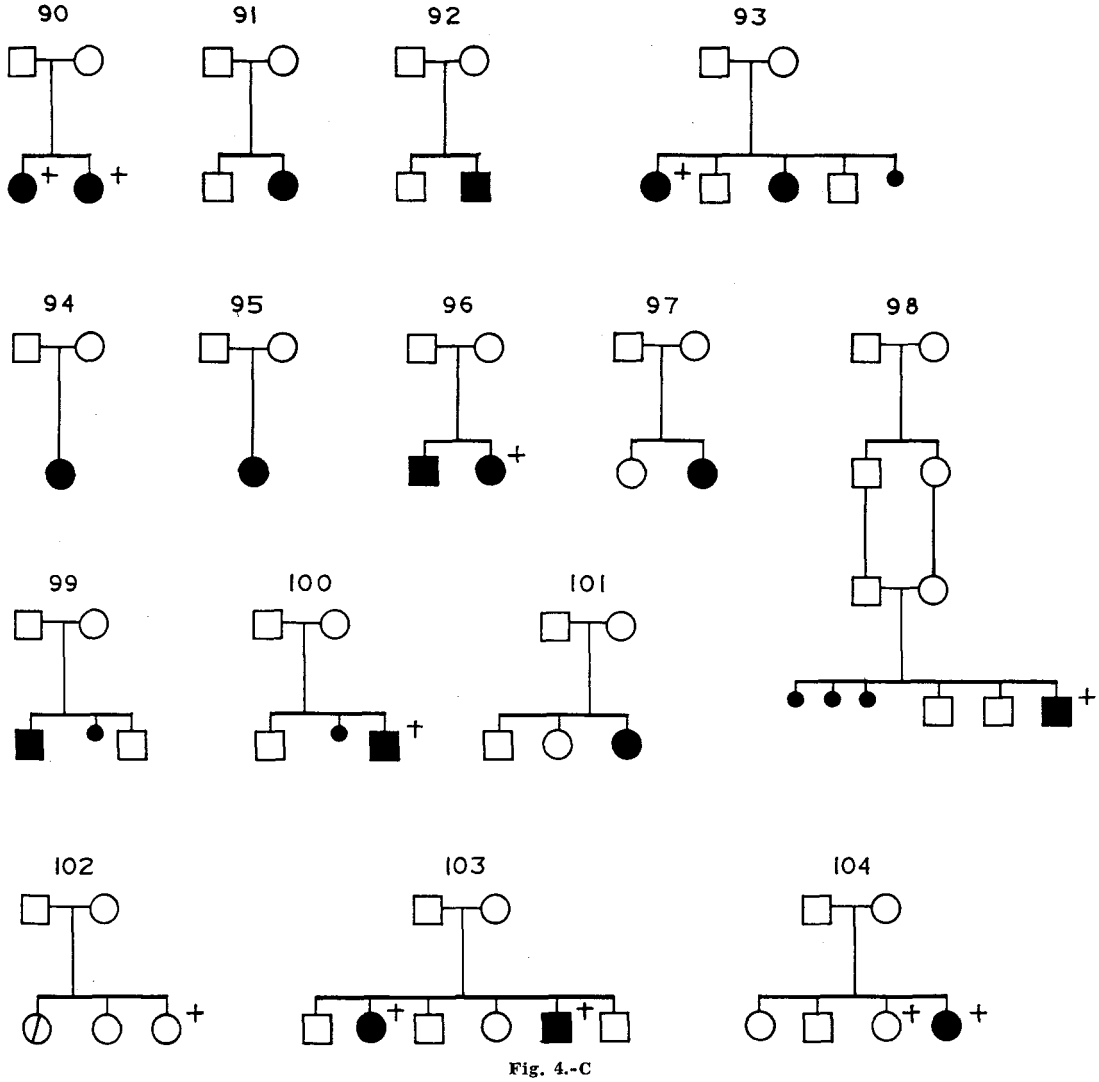

Fig. 4.-C

two who could not be traced to eastern Europe. These other two cases had ancestry in the Rhineland and in Austria. The parents were related in nine of the families; in five, the parents were first cousins.

It is the area of the so-called Jewish Pale in Lithuania, Poland and Russia where the Ashkenazic Jews who constitute the great majority of the Jews in this country lived in earlier centuries, and it is this same area where the ancestors of the dysautonomia cases lived. The question is how one accounts for this. I have been inclined to think that this was a matter of drift, that one of the founders who moved east from the Rhineland in the 1200's, driven by the pressure generated by the fervor of the Crusades, and drawn by the invitation from the King of Poland to settle in that area, carried this mutation. Perhaps this is not an adequate explanation. It presumes that the founding group was quite small. Recently Myranthopoulos and Aronson (1966), in connection with Tay-Sachs disease, which shows a rather similar picture although less strict limitation to Jews, have presented evidence which does not quite reach statistical significance but weakly suggests a heterozygous advantage for the person carrying the Tay-Sachs gene. Possibly something like this is occurring in the case of dysautonomia, but it is very difficult to know. Talking earlier today to Dr. Motulsky, it seems that it would be useful to try to get information on the size of the Jewish groups that moved from the Rhineland to the area of the subsequent Pale. It is planned to check on whether any concentration of ancestors is demonstrable in particular areas of Eastern Europe, as has been demonstrated for Tay-Sachs disease (1966).

Our method of ascertainment might be criticized as biased toward Jewish cases, but I doubt that this is a very serious bias. It

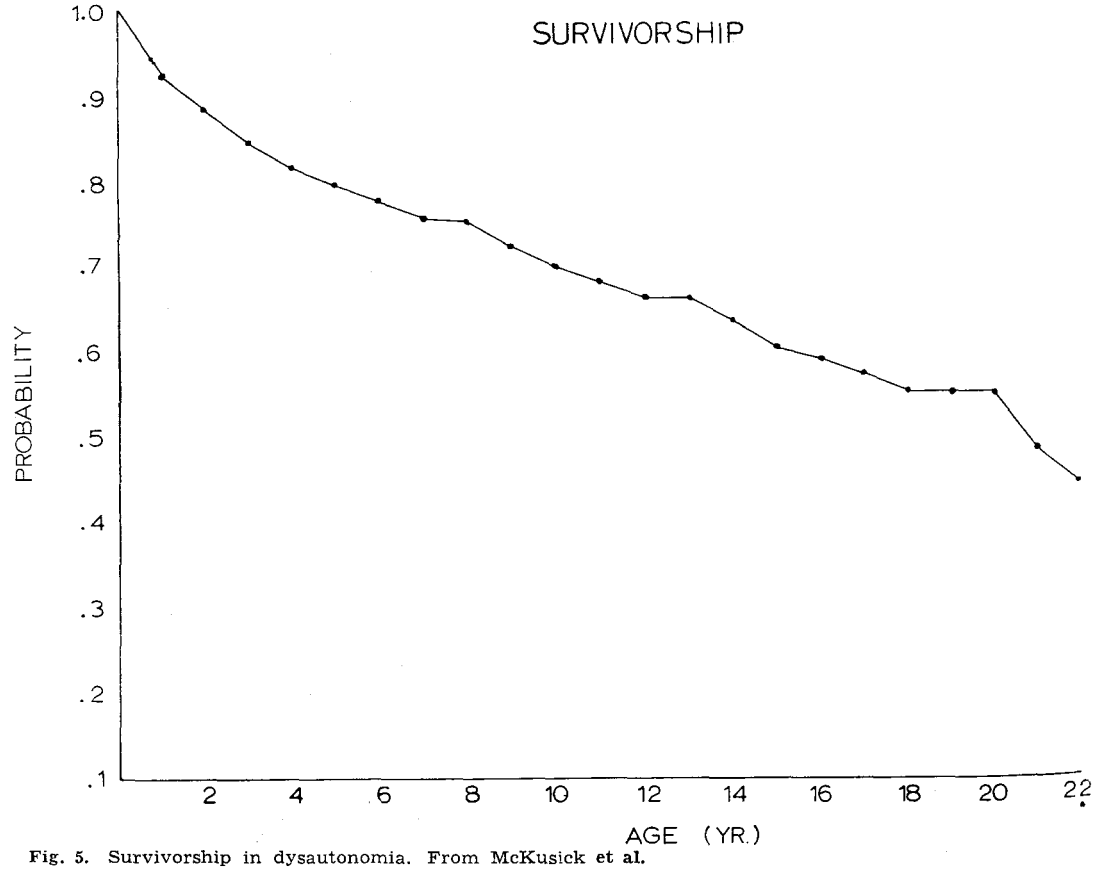

Fig. 5. Survivorship in dysautonomia. From McKusick et al.

TABLE 5

THE ETHNICITY OF DISEASE: SIMPLY INHERITED DISORDERS

Ethnic Group	*Relatively High Frequency*	*Relatively Low Frequency*
Ashkenazic Jews	Tay-Sachs disease Pentosuria Gaucher's disease Familial dysautonomia Stub thumbs Bloom's disease Factor XI (PTA) deficiency Niemann-Pick disease Abetalipoproteinemia Dystonia musculorum deformans Spongy degeneration of brain	Phenylketonuria
Mediterranean Peoples (Italians, Greeks, Sephardic Jews)	Thalassemia (mainly B) G6PD-deficiency, Mediterranean type Familial Mediterranean fever	Cystic fibrosis
Africans	Hemoglobinopathies, esp. HbS, HbC, α and β thal, persistent HbF G6PD-deficiency, African type	Cystic fibrosis Hemophilia Phenylketonuria Wilson's disease
Japanese (Koreans)	Acatalasia Oguchi's disease *Dyschromatosis universalis* hereditaria	
Chinese	α thalassemia G6PD-deficiency, Chinese type	
Armenians	Familial Mediterranean fever	

is true that this has been considered a Jewish disease from the beginning, and that Jewishness has been used almost as one of the criteria of diagnosis, but I think doctors in this country tend to be, by and large, iconoclasts and nothing would they delight in more than to be able to describe non-Jewish cases of this disease. I simply do not believe that many non-Jewish cases of this disease exist.

We estimate the frequency of this condition as between 1 in 10,000 and 1 in 20,000 births in American Jews. The frequency of Tay-Sachs disease has been estimated at 1 in 6,000. Pentosuria has been thought to have a frequency of one in every 2,500 births in American Jews. Tay-Sachs disease occurs in non-Jews but is about 100 times rarer. Pentosuria for practical purposes occurs only in Ashkenazic Jews, showing as rigid limitation to this group as does dysautonomia, perhaps more so. On the other hand, some recessive genes are less frequent in Jews. We know fewer that are less frequent because these are rare conditions and it is difficult to distinguish "very rare" from "rare," but phenylketonuria is essentially absent in American Jews.

Fig. 5 presents a survivorship curve on the dysautonomia cases. By age 10 over one-fourth of the cases are dead. By age 20 over half the cases are dead. This gives a minimal estimate of the gravity of the condition because it is possible that our ascertainment missed some of the more severe cases that died very early in life.

In Table 5 are listed some simply inherited disorders that have relatively high frequency or relatively low frequency in Americans of particular extraction. Cystic fibrosis is rare in persons of African extraction. Phenylketonuria is rare in the same group. Cystic fibrosis may be rarer in persons of Mediterranean extraction than in those from northern Europe, but this requires systematic study.

One can, of course, study the common disease of complex genetics from the point of view of ethnic extraction and some of these conditions are listed in Table 6.

It follows from what has been said that clinically it is diagnostically useful to focus on the ethnic extraction of patients.

Furthermore, it is important in connection with the description of any new recessive disease—any new inborn error of metabolism, for example—to record the ethnic extraction of the patients. Finally, with conditions such as cystic fibrosis, phenylketonuria, galactosemia and so on, it is useful to scrutinize, clinically and biochemically, the cases of various ethnic extractions as separate groups. Genetic heterogeneity, emphasized already in this conference in the case of G-6-PD deficiency and phenylketonuria, is likely to come to light when one keeps in mind the many ethnic groups that comprise the American population.

There is a need for the collation of historical, sociologic and biologic information on the groups which constitute the American people. A wealth of information is existent but is widely scattered. Giving thought to the best mechanism, I had thought the objective might be best achieved by a conference in which plenary sessions would be devoted to overall considerations and section meetings to individual ethnic groups or to individual topics. I have a comprehensive and necessarily large conference in mind. It might be a series of conferences. The objective of the conference would not be fulfilled without a written record. Indeed, a multi-authored book on the American people from the broad point of view we are discussing here is a possible way to do it. It has the disadvantage that no feedback and other interaction is possible and such would be important in an interdisciplinary undertaking of this type.

I am disturbed by the statement that

TABLE 6

THE ETHNICITY OF DISEASE: DISORDERS WITH COMPLEX GENETICS OR IN WHICH GENETIC FACTORS ARE NOT PROVED

Ethnic Group	*High Frequency*	*Low Freqnecy*
Ashkenazic Jews	Hypercholesterolemia	Cervical cancer
	Diabetes mellitus	Tuberculosis
	Polycythemia vera	Alcoholism
	Hyperuricemia	
	Ulcerative colitis and regional enteritis	
	Kaposi's sarcoma	
	Pemphigus vulgaris	
	Buerger's disease	
	Leukemia	
Northern Europeans	Pernicious anemia	
Chinese	Nasopharyngeal cancer	
Japanese	Cleft lip-palate	Otosclerosis
	Cerebrovascular accidents	Acne vulgaris
	Gastric carcinoma	Breast cancer
		Chronic lymphatic leukemia
Filipinos	Hyperuricemia	
Polynesians (Hawaiians)	Clubfoot	
Africans	Polydactyly	Major CNS malformations (anencephaly, encephalocele)
	Prehelical fissure	
	Sarcoidosis	
	Tuberculosis	Skin cancer
	Hypertension	Osteoporosis and fracture of hip
	Esophageal cancer	Polycythemia vera
	Uterine fibroids	Pyloric stenosis
	Corneal arcus	Gallstones
	Ainhum	
	Cervical cancer	
	Keloids	
American Indian and Mexican	Gallbladder disease	
	Tuberculosis	
Am. Indian, Lapps, No. Italian	Congenital dislocation of hip	
Icelanders	Glaucoma	
Eskimos	Salivary gland tumors	

ethnic extraction is a sensitive subject to a majority of present-day Americans. It is said, for example, that ethnic extraction is a topic so taboo that it would be politically inexpedient to propose an ethnicity question for the 1970 census schedules. I am not convinced that ethnic extraction is so sensitive a subject. Although one may raise questions as to the validity of the information—many people are uninformed on their ancestry—or questions about how the information would be collected and handled, there can be no question that ethnicity is an important variable in many sociologic and biologic considerations.

To paraphrase Dr. Dudley Duncan, we ought to recapture the spirit and language of earlier decades. The grand tradition of America of which we can justly boast is the creation of a nation from peoples literally of essentially all backgrounds.

Books such as Brown and Rouecek's *One America* and Witke's *We Who Built America* present very well, although necessarily briefly, the history of migration and assimilation and the contributions of the component groups of the American people.

I would like to see popular magazines devote more discussion to the marvelous cultural and biological heterogeneity of our country. Politicians should find the topic an advantageous one.

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Questions:

DR. ARNO MOTULSKY: I would like to make a couple of comments and I have one question. Sometimes these problems can be more complicated than initially thought. For instance, recently the rheumatology group in Seattle have been restudying the problem of hyperuricemia. They previously found that Filipinos living in Alaska had a higher uric acid level than white Caucasian people in Seattle. However, it turned out that people of higher social class apparently had higher uric acid levels, so it appears that there is a genetic difference which only comes out under the environment of a high diet. The high social class people and the workers who lived in Alaska and ate better than their compatriots in the Philippines did in fact have hyperuricemia. You would not detect it in the Philippines.

Another example of this sort might be something we have been studying some years ago in an experimental model. We have been struck by the rarity of hereditary spherocytosis in American Negroes. This never has been really carefully studied and may not be true, but it at least has been claimed, and clinically many people have said that they haven't seen very many cases and I haven't seen many cases in Negroes. I am wondering how this might come about. We thought that maybe since the red cell in this disease is sensitive to heat, possibly this disease might be at a greater disadvantage in a hot environment and therefore might not reach the frequency that is reached in Caucasian populations. So at that time we came across an animal model for this disease, a deer mouse with hereditary spherocytosis and put this to a test. We put normal deer mice and deer mice with hereditary spherocytosis in somewhat elevated environmental temperatures and found that within two or three weeks half of the spherocytic deer mice were dead of severe hemolytic crisis, while the slight-

ly elevated temperature did not bother at all the normal mice. So here we had again an example of the interaction of the genetic trait that didn't bother the spherocytic mice at room temperature—they were quite well, and you had to do special tests to show that they had spherocytosis—but if you just raised the temperature a little bit, they became severely sick and half of them died within a few weeks.

The question I have is: In your non-Jewish cases of dysautonomia, were they consanguineous as was shown in Tay-Sachs disease? Since that is more common in Jews, the consanguinity rate would be expected to be higher among non-Jews because there the trait would be rarer and it is more likely that two consanguineous people would inherit it from the same ancestry.

DR. McKUSICK: I think you misunderstood my statement of the data. There were two families in which the father was indeed Jewish and the mother was non-Jewish and they were apparently nonconsanguineous. I think the Filipino experience with hyperuricemia illustrates what I was commenting on, one of the approaches to the ethnicity of disease, a comparison of groups in this country with the homeland, and this particularly obtains with multifactorial conditions. I am not prejudicing the view as to whether hyperuricemia is multifactorial, but in those conditions it will be useful to use this approach to sort out the environmental factors as you have pointed out. In the case of hereditary spherocytosis, would you agree, Arno, that the mouse spherocytosis probably is not a very good replica of the human disease; in view of its recessive inheritance, it probably has an enzyme defect when the truth is known, whereas it begins to look, does it not, as though hereditary spherocytosis in man, a dominant condition, has a structural defect of the red cells?

DR. MOTULSKY: Well, pathophysiologically, the two diseases are exactly alike, since they both have the similar shortened survival, enlarged spleens, splenectomy cures the disease in man and mouse, and they both have increased heat sensitivity *in vitro,* so from gross pathophysiological criteria they are the same. However, the human disease is dominant, and so far the specific defect, as far as I know, is not clear. It seems to me, putting all the many data together, that the most likely possibility is some defect in the red cell stroma, the red cell membrane, and there are some suggestions of that. There are no ideas at all of what the defect might be in the mouse. If one would generalize, as you did, maybe it is an enzyme defect, but it could be a stromal defect too, that takes a double gene to produce the disease, so I think we will have to wait until we know more about that.

DR. ELLIOT VESSELL: What was the geographical distribution of the cases with familial dysautonomia?

DR. McKUSICK: Very wide indeed and it follows very closely the distribution of Jewry in this country. We probably have ten cases in the Los Angeles area. We have cases in Toronto, Montreal, Miami and so on and other scattered cases all over the United States map. The largest concentration of cases, of course, is in the New York area. I might say that the 164 that we have been able to study so far is a pretty wide geographic sampling of the some 220 that we have leads on.

DR. MARGARET BATSON: How conservative, how othodox are these people?

DR. McKUSICK: I think they cover the whole spectrum in this regard.

DR. DAVID SMITH: There seemed to be in the rapid view of the pedigrees quite a few abortions. Could you comment on that, please?

DR. McKUSICK: Yes, one of our field workers was much impressed with that and thought that she had a find. Perhaps she does. On counting them up, they aren't too impressive. I am sorry I can't give you the precise figures. We didn't have good figures to compare it with. I think this is an indication of very good interviewing and not an indication of any increased frequency of abortion in these families.